Remarks

In view of the above amendments and the following remarks, favorable reconsideration of the outstanding office action is respectfully requested. Claims 8-18 have been canceled. New claims 24-39 have been added. Claims 1-7, and 19-23 have been withdrawn from consideration, without prejudice.

1. § 112 Rejections

The Examiner rejects claims 8-18 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner asserts that claim 8 is indefinite because there is no nexus between the purpose in the preamble and the claimed steps, since none of the claim steps states that the goal is accomplished.

Applicant has rewritten the claims for sake of clarity and has provided a nexus between the preamble and the claim steps. In view of the changes indicated, Applicant believes that the basis for the Patent Office's rejection is remedied and the claims presently at issue are allowable.

2. § 102 Rejections

The Examiner rejects claims 8-12 and 16-18 under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 5,807,522 (Brown '522 patent). The Examiner alleges that Brown '522 teaches a method of microarray preparation and use that comprises all of the limitations of claims 8-12 and 16-18.

To anticipate under 35 U.S.C. § 102, a patent reference must "describe" every element recited in the claims at hand. The sections of the reference to which the Examiner refers does not carry this burden. The Brown '522 patent teaches a method for forming a microarray of discrete analyte-assay regions on a solid support; but, it neither mentions nor addresses the problem of reducing autofluorescence on a substrate, which is the method being claimed. To anticipate the present invention, the Brown '522 patent must disclose each and every claimed element. The reference, however, does not describe a reducing agent that eliminates autofluorescence on a substrate surface having not only an attached biological or synthetic molecule, but also a plain substrate surface that may be either coated or uncoated with particular functional groups for attachment chemistry. Hence, Applicant respectfully

submits that the Examiner has misread the reference, and requests that the rejection be withdrawn.

3. § 103 Rejections

The Examiner rejects claims 8-18 under 35 U.S.C. § 102(b) as being anticipated by or, in the alternative, under 35 U.S.C. § 103(a) as obvious over the article by Schena *et al.*, in the Proc. Nat'l. Acad. Sci. USA, vol. 93, pp. 10614-10619, (Oct. 1996). Acknowledging that the authors do not explicitly teach the limitations set forth in the claimed purpose, i.e. reducing autofluorescence on a substrate, the Examiner nonetheless alleges that Schena *et al.* teaches a method of preparing a microarray comprising all of the limitations of claim 8, and that the method inherently reduces autofluorescence on a substrate containing an array of biomolecules.

The article by Schena *et al.*, standing alone, cannot justify a *prima facie* case of obviousness or anticipation, since it neither suggests nor discloses all of the claimed limitations. Applicant respectfully submits that the Examiner has misinterpreted the reference. The Examiner cites, for example, the first full paragraph in the right-hand column on p. 10614, or the fourth full paragraph in the right-hand column on p. 10618, where Schena *et al.* write:

> "This 10-fold increase in sensitivity compared with the original report (4) [i.e., Schena *et al.* Science, vol. 270, pp. 467-470, 20 Oct. 1995] was achieved largely by modifying the coupling chemistry, which reduce background fluorescence."

One of ordinary skill in the art, however, would understand the term "coupling chemistry" to refer to the linkages between probe or target molecules.

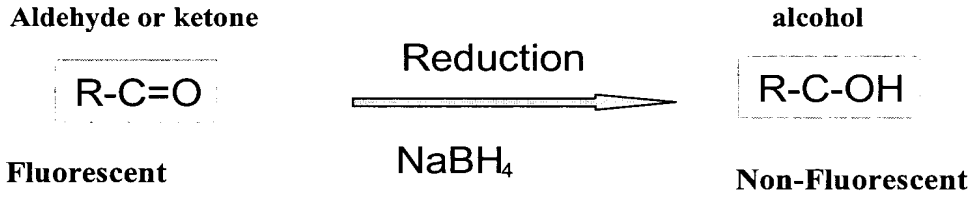
A brief explanation or clarification of terminology may be helpful in the present context. Generally, as understood by those skilled in the area, the term "background" refers to nonspecific signals, not the intrinsic auto-fluorescence of the substrate. Residual fluorescence may originate from either (1) nonspecific hybridization of probes with targets, or from (2) endogenous sample constituents, or (3) the substrate surface to which the biological or synthetic molecule is immobilized. Typically, background fluorescence signals, such as Schena *et al.* describe, can be eliminated through a high-stringency, post-hybridization wash of the arrays. The intrinsic auto-fluorescence of the substrate, however, can not be so easily eliminated. Applicant's claimed invention describes a method by which

this second type of auto-fluorescence is reduced significantly, by at least an order of magnitude, when the substrate is either a plain or coated with functional groups for immobilizing molecules, or on which molecules have already been attached.

Background signals can severely compromise sensitivity of fluorescence detection. Intrinsic auto-fluorescence of the array substrate can obscure the sensitivity of gene expression analysis by hindering the detection of the low-level specific fluorescent signals. Past attempts by other to diminish or eliminate auto-fluorescence through a variety of ways, such as by selecting filters that reduce the transmission of emission relative to excitation wavelength or by selecting probes that absorb and emit at longer wavelengths, have been found to be unsatisfactory. Further, although it increases the resolution, narrowing the fluorescence detection bandwidth also compromises the overall fluorescence intensity detected. Using probes, which can be excited at > 500 nm, has minimized to an extent but not completely the signal distortion which auto-fluorescence of arrays causes. Curing slides by baking at high temperatures in an oven was also found to be ineffective. Hence, a long felt needs exits in the area.

In principle, fluorescence is caused by an aptly conjugated electronic system in an organic molecule. Auto-fluorescence may be due to trace impurities of such molecules that typically contain single or conjugated pi bonding. Moreover, during storage or printing, oxidation of some biological or chemical contaminants could result in the emission of fluorescence (e.g., FIG. 1).

FIG. 1



Briefly washing the arrays for 5 minutes with a solution of 0.25% $NaBH_4$ by volume does not significantly reduce the second type of auto-fluorescence. (See for comparison Fig. 8 in Applicant's specification.) Since Schena *et al.* either do not discuss the problem of intrinsic auto-fluorescence or were not concerned about the problem, then, logically, Schena *et al.* cannot have taught a method of reducing auto-fluorescence.

For the foregoing reasons, Applicant submits that the Examiner may properly withdraw the present rejection.

4. Conclusion

Based upon the above amendments, remarks, and papers of record, Applicant believes the pending claims of the above-captioned application are in allowable form and patentable over the prior art of record. Applicant respectfully requests reconsideration of the pending claims and a prompt Notice of Allowance thereon.

Applicant believes that no extension of time is necessary to make this Response timely. Should Applicant be in error, Applicant respectfully requests that the Office grant such time extension pursuant to 37 C.F.R. § 1.136(a) as necessary to make this Reply timely, and hereby authorizes the Office to charge any necessary fee or surcharge with respect to said time extension to the deposit account of the undersigned firm of attorneys, Deposit Account 03-3325.

Please direct any questions or comments to Vincent T. Kung at (607) 974-0608.

Respectfully submitted,

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VERSION OF MARKINGS TO SHOW CHANGES MADE

1. (Withdrawn) A method of immobilizing biomolecules on a surface of a substrate comprising:

providing a substrate having a first surface including a functional group for non-covalent attachment to a biomolecule;

contacting at least a portion of the first surface with a reducing agent;

attaching a biomolecule to the functional group.

2. (Withdrawn) The method of claim 1, wherein the reducing agent includes a hydride.

3. (Withdrawn) The method of claim 1, wherein the reducing agent includes a borohydride.

4. (Withdrawn) The method of claim 3, wherein the borohydride includes sodium borohydride.

5. (Withdrawn) The method of claim 4, wherein the sodium borohydride is in a solution at a concentration ranging from 0.01% to 1% by volume.

6. (Withdrawn) A substrate made in accordance with the method of claim 2.

7. (Withdrawn) A substrate made in accordance with the method of claim.

8. (Cancelled) A method of reducing autofluorescence on substrate containing an array of biomolecules comprising:

providing a substrate having an array of target biomolecules non-covalently attached to at least a first surface of the substrate;

treating at least a portion of the first surface of the substrate with a reducing agent;

hybridizing complementary probe biomolecules to the biomolecules; and

scanning the substrate.

9. (Cancelled) The method of claim 8, wherein the complementary probe biomolecules are labeled with a fluorescent label.

10. (Cancelled) The method of claim 9, wherein the step of scanning the substrate includes scanning the substrate for the fluorescent label.

11. (Cancelled) The method of claim 10, wherein the reducing agent includes hydrogen.

12. (Cancelled) The method of claim 11, wherein the reducing agent includes a hydride.

13. (Cancelled) The method of claim 12, wherein the reducing agent includes a borohydride.

14. (Cancelled) The method of claim 13, wherein the step of treating the substrate with a reducing agent includes contacting at least a portion of the first surface of the substrate with an aqueous solution containing between 0.1 and 1% sodium borohydride by volume.

15. (Cancelled) The method of 14 wherein the aqueous solution contains between 0.2% and 0.3% sodium borohydride by volume.

16. (Cancelled) A substrate having an array of biomolecules non-covalently attached thereto produced by the method of claim 8.

17. (Cancelled) The substrate of claim 16, wherein the biomolecules are nucleic acids or oligonucleotides.

18. (Cancelled) The substrate of claim 17, wherein the substrate is contains high density array of nucleic acids or oligonucleotides.

19. (Withdrawn) A method of eliminating autofluorescensce from a substrate coated with a silane comprising treating at least a portion of a first surface of the slide with a reducing agent.

20. (Withdrawn) The method of claim 19, wherein the silane coating includes an amino-silane.

21. (Withdrawn) The method of claim 20, wherein the silane coating includes gamma-amino-propyl-silane

22. (Withdrawn) The method of claim 20, wherein the reducing agent includes a hydride.

23. (Withdrawn) The method of claim 22, wherein the reducing agent includes sodium borohydride.

24. (New) A method for reducing auto-fluorescence on a substrate, the method comprising:

providing a substrate with at least a first surface, said first surface being either with or without either a biological or a synthetic molecule immobilized thereon, or having either a coated or uncoated surface with a residual fluorescence; and

treating at least a portion of the first surface of the substrate with a reducing agent for longer than about 5 minutes to reduce auto-fluorescence on the substrate.

25. (New) The method of claim 24, wherein the reducing agent includes hydrogen.

26. (New) The method of claim 24, wherein the reducing agent includes a hydride.

27. (New) The method of claim 26, wherein the reducing agent includes a borohydride.

28. (New) The method of claim 24, wherein the step of treating the substrate with a reducing agent includes contacting at least a portion of either the active or first surface of the substrate with an aqueous solution containing between 0.1 and 1% sodium borohydride by volume.

29. (New) The method of claim 28, wherein the aqueous solution contains between 0.2% and 0.3% sodium borohydride by volume.

30. (New) The method of claim 24, wherein said autofluorescence is reduced by at least an order of magnitude RFU.

31. (New) The method of claim 24, wherein said substrate is treated for at least 10 minutes with said reducing agent.

32. (New) The method of claim 24, further comprising a step of scanning the substrate.

33. (New) The method of claim 32, wherein said canning step includes scanning the substrate for a fluorescent label.

34. (New) The method of claim 24, wherein said substrate is made from a material selected from the group consisting of inorganic materials, glass, ceramic materials, metals, and semiconductor materials.

35. (New) The method of claim 24, wherein said substrate is made from a material selected from the group consisting of organic materials, polyesters, polybutylene terephthalate, polyvinylchloride, polyvinylidene fluoride, polytetrafluoroethylene, polycarbonate, polyamide, poly(meth)acrylate, polystyrene, polyethylene or ethylene/vinyl acetate copolymer.

36. (New) The method of claim 24, wherein said biological or synthetic molecule includes at least one of the following species: ribonucleic acids (RNA), deoxyribonucleic acids (DNA), synthetic oligonucleotides, antibodies, proteins, peptides, lectins, modified polysaccharides, cells, synthetic composite macromolecules, functionalized nanostructures, synthetic polymers, modified/blocked nucleotides/nucleosides, modified/blocked amino acids, fluorophores, chromophores, ligands, chelates, and haptens.

37. (New) A substrate having an array of biomolecules non-covalently attached thereto produced by the method of claim 24.

38. (New) The substrate of claim 24, wherein the biomolecules are nucleic acids or oligonucleotides.

39. (New) The substrate of claim 24, wherein the substrate is contains an array of nucleic acids or oligonucleotides